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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/643,197	08/22/2000	PASCAL DESMAZEAU	ST98007 US	8404

7590 02/21/2003

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	17

DATE MAILED: 02/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/643,197	Desmazeau
Examiner	**Art Unit**
David Lukton	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 8, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *18-34* is/are pending in the application.

4a) Of the above, claim(s) *31* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *18-30 and 32-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *12, 13*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 9 (filed 3/11/02), claims 18 and 31 have been amended. Claims 18-34 remain pending.

Applicants' election of Group IV (claims 18-30, 32-34) with traverse is acknowledged, as is the elected specie.

Applicants have argued that the examiner has provided no reasons for the restriction. However, this was done in the previous Office action. Compounds of claim 31 are known in the prior art, and the invention of claim 31 does not "define a contribution" over the prior art. However, if applicants believe that claim 31 does "define a contribution" over the prior art, applicants are invited to make an admission that the invention of Group IV is obvious over the invention of Group V and *vice versa*. If this is done, the restriction requirement will be reconsidered. It is maintained at the present time, however.

*

An abstract has been submitted. However, the (one) sentence of the abstract is grammatically incorrect. One way of rectifying this deficiency would be to state the following:

Group A streptogramin derivatives of formula I are disclosed...

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-30, 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is asserted in the specification that the claimed compounds are effective to inhibit growth of bacteria. However, there is no evidence that this is the case. As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, structure/activity relationships of antibacterial compounds are unpredictable. Consider, for example, the following:

- Gavini ("Pyridazine N-oxides. III. Synthesis and in vitro antimicrobial properties of N-oxide derivatives based on tricyclic indeno[2,1- c]pyridazine and benzo[f]cinnoline systems", *Archiv der Pharmazie* **333** (10) 341-6, 2000) discloses the preparation and testing of a series of pyridazine N-oxides. With the exception of compounds 3a, 3b, 4b and 5b, the compounds "demonstrated no activity against bacteria" (page 342, col 2).

- Fudou ("Haliangicin, a novel antifungal metabolite produced by a marine

myxobacterium. 1. Fermentation and biological characteristics", *Journal of Antibiotics* **54** (2) 149-52, 2001) discloses the isolation of haliangicin which is produced by a marine bacteria; the compound contains a conjugated tatraene moiety and exhibited no antibacterial activity.

- Juvvadi ("Structure-activity studies of normal and retro pig cecropin-melittin hybrids", *Journal of Peptide Research* **53** (3) 244-51, 1999) discloses the preparation and antibacterial activity of cecropin-melittin hybrid peptides. Also disclosed is that the "retro" analogs (the polarity of the amide bond reversed) lost antibacterial activity.

- Avrahami (*Biochemistry* **40** (42) 12591-603, 2001) studied the effects of amino acid substitutions on the antimicrobial activity of amphipathic antimicrobial peptides. Many of the compounds prepared lost antibacterial activity as a result of a single amino acid substitution. Although after-the-fact rationalizations were provided, the observed structure/ activity relationships could not have been predicted *a priori*.

These and other references disclose that there do exist compounds which exhibit no antibacterial activity, and many of these inactive compounds are structurally analogous to compounds that are active. The key point is that the factors which give rise to activity or inactivity are unknown in the art; and certainly applicants have made no attempt to discuss such factors.

With regard to the "pharmaceutical composition", this term carries with it the implied assertion of therapeutic efficacy. Even if applicants were to provide *in vitro* data, extrapolation to treatment of ill patients would not be enabled. Diseases caused by bacteria include the following:

> Anthrax, Bovine Spongiform, Encephalopathy (BSE), Chicken Pox, Cholera, Conjunctivitis, Creutzfeldt-Jakob Disease, Polio, Nosocomial Infections, Otitis Media, Pelvic Inflammatory disease, Plague, Pneumonia, Dengue Fever, Elephantiasis,

Encephalitis, Fifth's Disease, Rabies, Rheumatic Fever, Roseola, Rubella, Sexually Transmitted diseases, Helicobacter Pylori, Smallpox, Strep Throat, septicemia, sickle cell anemia, ulcers, Tetanus, Toxic Shock Syndrome, Lassa Fever, Leprosy, Lyme Disease, Typhoid Fever, Measles, Meningitis, Trachoma, Toxoplasmosis, Tuberculosis, Whooping Cough, Yellow Fever

Which of these, exactly, do applicants believe that they can treat? If the patient is afflicted with AIDS (in addition to a bacterial infection), are the claimed compounds effective? In addition, there is the problem of antibiotic resistance. Presumably applicants are aware of this, but if not, the following two articles discuss this matter:

Liu (*Advances in Experimental Medicine and Biology* **455**, 387 1999)

Monroe (*Current Opinion in Microbiology* **3**(5) 496-501, 2000).

Accordingly, (a) one cannot predict antibacterial activity merely by viewing a structure, (b) "undue experimentation" would be required to determine which of the claimed compounds will inhibit bacterial growth, and (c) even if it were true that the compounds exhibited antibacterial activity *in vitro*, "undue experimentation" would be required to determine which of the claimed compounds can be used to treat even <u>one</u> disease caused by bacteria, to say nothing of the considerable number of diseases that one would have to test for therapeutic efficacy against.

It is noted that on page 33, there is a vague assertion that if one combines one of the claimed compounds with a compound that is known in the prior art to inhibit bacterial

growth, the result is that the claimed compound does not diminish the antibacterial activity that is known to exist for the prior art compound. However, this proves nothing about the propensity of the claimed compounds to inhibit bacterial growth.

It is suggested that applicants provide at least *in vitro* data that establishes the bacterial growth inhibitory efficacy that has been asserted; also suggested is that the term "pharmaceutical" be deleted from whichever claims recite it.

*

Claims 26-30, 32-33 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Each of claims 26-30 is rendered indefinite by its failure to recite a step for isolating the final product (the compound of claim 18). At the end of the reaction processes, one will be left with a round-bottom flask containing the target compound, solvent, starting materials, and various impurities. If a chemist abstains from isolating the target compound from this mixture, then he is not in possession of the final product. To equate a mixture with a pure compound is simply an invalid proposition. It is suggested that each of claims 26-30 recite a step for isolation of the final product.

- Claim 32 characterizes diluents and adjuvants as "agents". However, the term "agent" is normally associated with the biologically active ingredient, rather than the inactive carrier. Accordingly, use of term in this way is misleading.

- Claim 32 recites that the presence of diluents and adjuvants is "optional", and that the presence of the Group B streptogramin is also optional. Thus, claim 32 encompasses the possibility of the composition comprising a compound according to claim 18, but at the same time, excluding all of the following: (a) a diluent, (b) an adjuvant, and (c) a Group B streptogramin. For this specific case, the claim is indefinite. A composition requires at least two components. Thus, claim 32

mandates the presence of a compound (or mixture of compounds) in addition to the compound of claim 18, yet permits that compound (or mixture of compounds) to be something other than a diluent an adjuvants or a Group B streptogramin. What are the other options?

- Claim 26 is indefinite as to the objective and conditions of step (a). The claim encompasses process in which the time and conditions are not effective to form a compound of formula I. For example, if the two reactants are combined in tetrahydrofuran at -20 °C for a period of 10 seconds, does the compound of claim 18 form spontaneously? At the other end of the spectrum, if the two reactants are heated at a temperature of 250 °C for a period of 96 hours in the presence of oxygen, will one be able to isolate any of the compound of claim 18...? It is suggested that the claim be amended to recite that time and conditions are indeed effective to form a compound according to claim 18.

- Claim 33 makes reference to various group A streptogramin derivatives such as pristinamycin II_B. However, this renders the claim indefinite. It is suggested that a chemical name or structure be provided for each of the listed compounds.

✺

The three patent applications listed on the IDS were stricken because a copy was not provided.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800